



STIC Search Report

Biotech-Chem Library

STIC Database Tracking Number: 102680

TO: Phyllis Spivack
Location: 1/2d01
Art Unit: 1614
Friday, August 29, 2003

Case Serial Number: 10/055915

From: Mary Hale
Location: Biotech/Chem Library
CM1-1E01
Phone: 308-4258

Mary.Hale@uspto.gov

Search Notes

S arched-

Structure, had to modify after reviewing one hit and noticed nitrogen was missing from drawn structure.

S arched-

Synonyms for depression....

Searched- therap? Or treatment

Searched- inventor

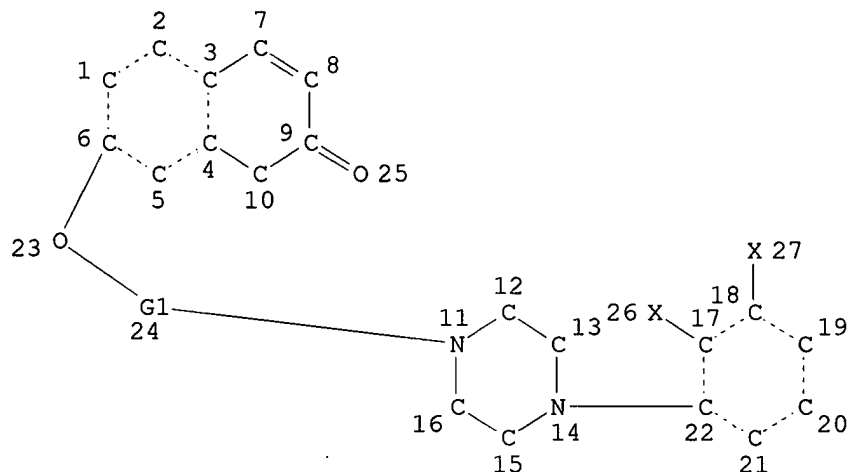
(+)8-OH,DPAT activity. 5-HT and (+)8-OH,DPAT stimulated basal (35S)GTP-gamma-S binding to h5-HT1A membranes by > 2-fold, while (-)8-OH,DPAT, buspirone, OPC-14523, and NAN-190 displayed partial agonist efficacies. These drug effects were all blocked by WAY-100635, which was inactive on its own. The present data identify OPC-14523 as a partial agonist at rat and human 5-HT1A receptors.

L52 ANSWER 8 OF 8 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN 1997:235584 Document No.: PREV199799534787. **Antidepressant** effect of OPC-14523 in the forced swimming test in mice. Tottori, Katsura; Kikuchi, Tetsuro; Uwahodo, Yasufumi; Yamada, Sakiko; Oshiro, Yasuo; Koga, Nobuyuki. Third Tokushima Inst. New Drug Res., Otsuka Pharmaceutical Co. Ltd., Tokushima 771-01 Japan. Japanese Journal of Pharmacology, (1997), Vol. 73, No. SUPPL. 1, pp. 59P. Meeting Info.: 70th Annual Meeting of the Japanese Pharmacological Society Chiba, Japan March 22-25, 1997 ISSN: 0021-5198. Language: English.

=> del his y

Spwack
10/055915

=> d 13 que stat;d 16 que stat;e "5ht1a"/cn
L1 STR



REP G1=(4-4) CH2
NODE ATTRIBUTES:
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

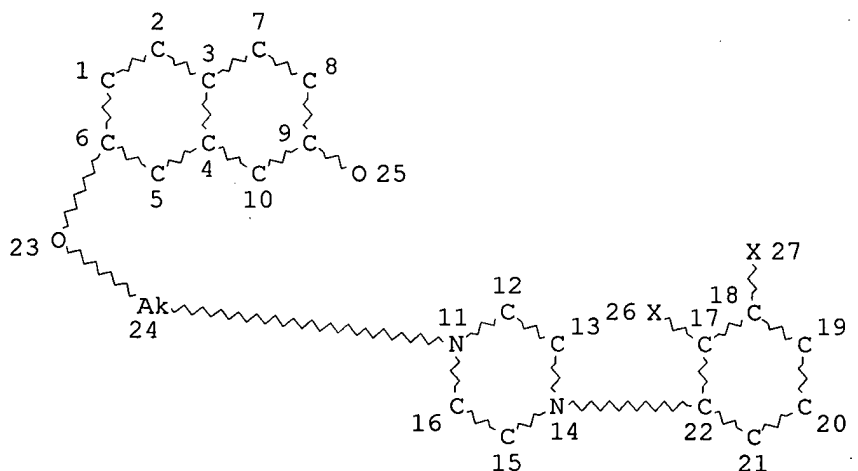
GRAPH ATTRIBUTES:
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NUMBER OF NODES IS 27

STEREO ATTRIBUTES: NONE
L3 0 SEA FILE=REGISTRY SSS FUL L1

100.0% PROCESSED 1 ITERATIONS
SEARCH TIME: 00.00.02

0 ANSWERS

L4 STR



NODE ATTRIBUTES:
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

Searched by: Mary Hale 308-4258 CM-1 1E01

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS 27

STEREO ATTRIBUTES: NONE
L6 0 SEA FILE=REGISTRY SSS FUL L4

100.0% PROCESSED 16840 ITERATIONS 0 ANSWERS
SEARCH TIME: 00.00.01

E1	1	5HNM/CN
E2	1	5HS/CN
E3	0 -->	5HT1A/CN
E4	1	5I20AC/CN
E5	1	5I23/CN
E6	1	5I30/CN
E7	1	5IAF/CN
E8	1	5IUDR/CN
E9	1	5J11/CN
E10	1	5J16/CN
E11	1	5J18/CN
E12	1	5K0.4/CN

=> fil medl,hcaplus,biosis,embase,wpids
COST IN U.S. DOLLARS

SINCE FILE	TOTAL
ENTRY	SESSION
298.30	298.51

FULL ESTIMATED COST

FILE 'MEDLINE' ENTERED AT 10:06:01 ON 29 AUG 2003

FILE 'HCAPLUS' ENTERED AT 10:06:01 ON 29 AUG 2003
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FILE 'WPIDS' ENTERED AT 10:06:01 ON 29 AUG 2003
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=> s (5ht1a or 5ht?) and receptor

L7	1783	FILE MEDLINE
L8	4260	FILE HCAPLUS
L9	2777	FILE BIOSIS
L10	2077	FILE EMBASE
L11	578	FILE WPIDS

TOTAL FOR ALL FILES

L12 11475 (5HT1A OR 5HT?) AND RECEPTOR

=> s l12 and (treat? or therap? or prevent?) and (depress? or antidepress? or
thymoanaleptic? or thymoleptic? or monoamine oxidase inhibit?)

Searched by: Mary Hale 308-4258 CM-1 1E01

L13 143 FILE MEDLINE
 L14 437 FILE HCAPLUS
 L15 161 FILE BIOSIS
 L16 209 FILE EMBASE
 L17 283 FILE WPIDS

TOTAL FOR ALL FILES

L18 1233 L12 AND (TREAT? OR THERAP? OR PREVENT?) AND (DEPRESS? OR ANTIDEP
 RESS? OR THYMOANALEPTIC? OR THYMOLEPTIC? OR MONOAMINE OXIDASE
 INHIBIT?)

=> s l18 and (jordan, s? or jordan s? or kikuchi t? or kikuchi, t?)/au,in
 'IN' IS NOT A VALID FIELD CODE

L19 0 FILE MEDLINE
 L20 1 FILE HCAPLUS
 L21 0 FILE BIOSIS
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 L22 0 FILE EMBASE
 L23 0 FILE WPIDS

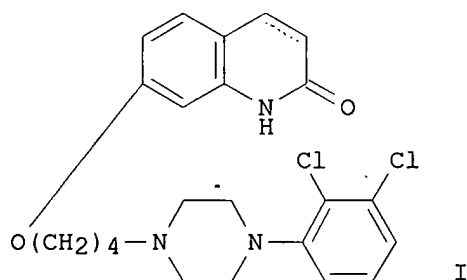
TOTAL FOR ALL FILES

L24 1 L18 AND (JORDAN, S? OR JORDAN S? OR KIKUCHI T? OR KIKUCHI, T?)/A
 U,IN

=> d cbib abs

L24 ANSWER 1 OF 1 HCAPLUS COPYRIGHT 2003 ACS on STN
 2002:594663 Document No. 137:150248 Carbostyryl derivative 5-HT1a
receptor agonists for **treatment** of central nervous
 system disorders. **Jordan, Shaun**; Kikuchi, Tetsuro; Tottori,
 Katsura; Hirose, Tsuyoshi; Uwahodo, Yasufumi (Otsuka Pharmaceutical Co.,
 Ltd., Japan). PCT Int. Appl. WO 2002060423 A2 20020808, 31 pp.
 DESIGNATED STATES: W: AU, BR, CA, CN, ID, IN, JP, KR, MX, PH, SG; RW: AT,
 BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR.
 (English). CODEN: PIXXD2. APPLICATION: WO 2002-JP626 20020129.
 PRIORITY: US 2001-770210 20010129.

GI



AB The invention discloses the use of a compd. for the prodn. of a medicament
 for **treating** a patient suffering from a disorder of the central
 nervous system assocd. with 5-HT1a **receptor** subtype, the
 medicament including as an active ingredient a carbostyryl deriv. I (C-C
 bond between 3- and 4-positions in the carbostyryl skeleton is single or
 double bond), or a pharmaceutically acceptable salt or solvate thereof.

=> fil reg

COST IN U.S. DOLLARS

SINCE FILE

TOTAL

ENTRY

SESSION

FULL ESTIMATED COST

11.71

310.22

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)

SINCE FILE

TOTAL

ENTRY

SESSION

CA SUBSCRIBER PRICE

-0.65

-0.65

FILE 'REGISTRY' ENTERED AT 10:08:56 ON 29 AUG 2003

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STRUCTURE FILE UPDATES: 27 AUG 2003 HIGHEST RN 574700-05-3

DICTIONARY FILE UPDATES: 27 AUG 2003 HIGHEST RN 574700-05-3

TSCA INFORMATION NOW CURRENT THROUGH JANUARY 6, 2003

Please note that search-term pricing does apply when conducting SmartSELECT searches.

Crossover limits have been increased. See HELP CROSSOVER for details.

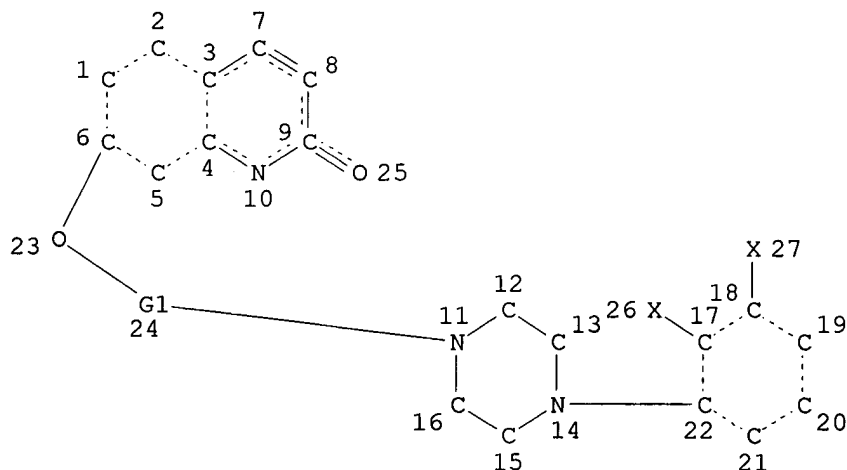
Experimental and calculated property data are now available. See HELP PROPERTIES for more information. See STN Note 27, Searching Properties in the CAS Registry File, for complete details:

<http://www.cas.org/ONLINE/STN/STNOTES/stnotes27.pdf>

=> d 127 que stat

L25

STR



REP G1=(4-4) CH2

NODE ATTRIBUTES:

DEFAULT MLEVEL IS ATOM

DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:

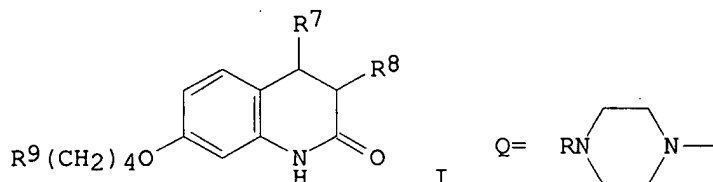
RING(S) ARE ISOLATED OR EMBEDDED

NUMBER OF NODES IS 27

Searched by: Mary Hale 308-4258 CM-1 1E01

REFERENCE 4: 113:152468 Preparation and formulation of 7-[(4-phenylpiperazino)butoxy]carbostyrils as dopaminergic neurotransmitter antagonists. Oshiro, Yasuo; Sato, Seiji; Kurahashi, Nobuyuki (Otsuka Pharmaceutical Co., Ltd., Japan). Eur. Pat. Appl. EP 367141 A2 19900509, 27 pp. DESIGNATED STATES: R: CH, DE, ES, FR, GB, IT, LI, NL, SE. (English). CODEN: EPXXDW. APPLICATION: EP 1989-120001 19891027. PRIORITY: JP 1988-276953 19881031.

GI



AB The title compds. (I; R7, R8 = H; R7R8 = bond; R9 = piperazino group Q; R = 2-alkoxyphenyl, 3,5- or 2,3-dichloro- or 2,3-dibromophenyl, 2-methyl-3-nitrophenyl, etc.) were prepd. Thus, 7-hydroxy-3,4-dihydrocarbostyryl was refluxed 3 h with Br(CH2)4Br in aq. K2CO3 to give I (R7 = R8 = H, R9 = Br) which was refluxed 30 min with NaI in MeCN after which 1-(2,3-dichlorophenyl)piperazine was added and the whole refluxed 3 h to give I (R7 = R8 = H, R9 = Q, R = 2,3-Cl2C6H3) which had ED50 of 0.18 and >128 mg/kg orally for antiapomorphine and antiepinephrine activity, resp., in mice.

=> fil medl,hcaplus,biosis,embase,wpids
COST IN U.S. DOLLARS

SINCE FILE	TOTAL
ENTRY	SESSION
152.93	463.15

FULL ESTIMATED COST

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)

SINCE FILE	TOTAL
ENTRY	SESSION
-0.62	-1.27

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FILE 'MEDLINE' ENTERED AT 10:10:49 ON 29 AUG 2003

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=> s (5(w)htla or 5(w)ht?) and receptor

L28 16340 FILE MEDLINE

L29 20077 FILE HCAPLUS

Searched by: Mary Hale 308-4258 CM-1 1E01

L30 20558 FILE BIOSIS
L31 17574 FILE EMBASE
L32 1356 FILE WPIDS

TOTAL FOR ALL FILES

L33 75905 (5(W) HT1A OR 5(W) HT?) AND RECEPTOR

=> s l33 and (depress? or antidepress? or thymoanaleptic? or thymoleptic? or monoamine oxidase inhibit?)

L34 2600 FILE MEDLINE
L35 3049 FILE HCAPLUS
L36 2962 FILE BIOSIS
L37 2858 FILE EMBASE
L38 750 FILE WPIDS

TOTAL FOR ALL FILES

L39 12219 L33 AND (DEPRESS? OR ANTIDEPRESS? OR THYMOANALEPTIC? OR THYMOLEPTIC? OR MONOAMINE OXIDASE INHIBIT?)

=> s l39 and (jordan, s? or jordan s? or kikuchi t? or kikuchi, t?)/au,in
'IN' IS NOT A VALID FIELD CODE

L40 2 FILE MEDLINE
L41 4 FILE HCAPLUS
L42 6 FILE BIOSIS
'IN' IS NOT A VALID FIELD CODE
L43 2 FILE EMBASE
L44 2 FILE WPIDS

TOTAL FOR ALL FILES

L45 16 L39 AND (JORDAN, S? OR JORDAN S? OR KIKUCHI T? OR KIKUCHI, T?)/AU,IN

=> s l45 not l24

L46 2 FILE MEDLINE
L47 3 FILE HCAPLUS
L48 6 FILE BIOSIS
L49 2 FILE EMBASE
L50 2 FILE WPIDS

TOTAL FOR ALL FILES

L51 15 L45 NOT L24

=> dup rem l51

PROCESSING COMPLETED FOR L51

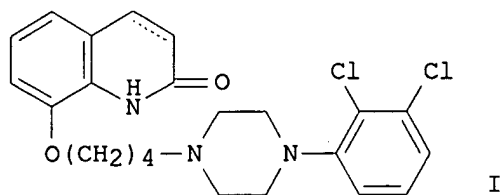
L52 8 DUP REM L51 (7 DUPLICATES REMOVED)

=> d cbib abs 1-8

L52 ANSWER 1 OF 8 HCAPLUS COPYRIGHT 2003 ACS on STN DUPLICATE 1
2002:889556 Document No. 137:363096 Carbostyryl derivative 5-
HT1a receptor subtype agonist for treatment of central
nervous system disorders. **Jordan, Shaun**; Kikuchi, Tetsuro;
Tottori, Katsura; Hirose, Tsuyoshi; Uwahodo, Yasufumi (USA). U.S. Pat.
Appl. Publ. US 2002173513 A1 20021121, 8 pp. (English). CODEN: USXXCO.
APPLICATION: US 2002-55915 20020128. PRIORITY: US 2001-PV331370 20010129.

GI

instant



AB The invention provides a method for treating a patient suffering from a disorder of the central nervous system assocd. with the 5-HT1a receptor subtype, comprising as an active ingredient a carbostyryl deriv. I (carbon-carbon bond between 3- and 4-positions in carbostyryl skeleton is single or double bond), or a salt thereof.

L52 ANSWER 2 OF 8 WPIDS COPYRIGHT 2003 THOMSON DERWENT on STN

AN 2002-682672 [73] WPIDS

AB WO 200260423 A UPAB: 20030723

NOVELTY - Disorders associated with 5-HT1A receptor subtype are treated using carbostyryl compound.

DETAILED DESCRIPTION - Disorders of the central nervous system associated with 5-HT1A receptor subtype are treated using carbostyryl compound of formula (I), its salt or solvate, in which the carbon-carbon bond between 3- and 4- positions in the carbostyryl skeleton is a single or double bond.

ACTIVITY - Central nervous system-Gen.; Antidepressant; Vasotropic; Antialcoholic; Nootropic; Neuroprotective; Antiparkinsonian; Tranquilizer; Anorectic; Antimigraine; Neuroleptic.

MECHANISM OF ACTION - 5-HT1A receptor subtype agonist. 7-(4-(4-(2,3-Dichlorophenyl)-1-piperazinyl)-butoxy)-3,4-dihydrocarbostyryl (test compound)/serotonin (5-HT)

(reference compound) was studied in triplicate at 10 different concentrations (0.01, 0.1, 1, 10, 50, 100, 500, 1000, 5000 and 10000 nM) to determine its displacement of (3H)8-OH-DPAT binding to h5-HT1A receptors in CHO cell membranes (15 - 20 micro g protein).

Membranes (396 micro l) were incubated in 5 ml glass tubes containing (63H)8-OH-DPAT (396 micro l), test compound or vehicle (8 micro l) and buffer A (Tris.HCl (50 mM), MgSO4 (10 mM), EDTA (0.5 mM), ascorbic acid (0.1% w/v), pH = 7.4). All assays proceeded for 60 minutes at room temperature and were terminated by rapid filtration, using a harvester and ice-cold washes with buffer B (Tris HCl (50 mM); pH = 7.4). Non-specific binding was determined in the presence of (+)8-OH-DPAT (10 micro M). The test/reference compound showed following results: potency (EC50, nM; 95% confidence interval) = 2.12 (0.87 - 5.16)/3.67 (1.50 - 8.63); intrinsic agonist efficacy (Emax % plus or minus SEM) = 68.13 plus or minus 3.16/98.35 plus or minus 4.47; goodness of fit (r2) = 0.986/0.986.

USE - For treating disorders of the central nervous system associated with 5-HT1A receptor subtype e.g.

depression (including endogenous depression, major depression, melancholia or treatment-resistant depression); sexual dysfunction; alcohol abuse and drug addiction; cognitive impairments; neurodegenerative disease including Alzheimer's disease or Parkinson's disease; autism, Down's syndrome, panic, obsessive compulsive disorder (OCD), sleep disorders, emesis, motion sickness, obesity or migraine), attention deficit hyperactivity disorder; treatment-resistant schizophrenia, inveterate schizophrenia, or chronic schizophrenia with cognitive impairments, which fails to respond adequately to currently

available antipsychotic drugs (preferably drugs are chlorpromazine, haloperidol, sulpiride, fluphenazine, perphenazine, thioridazine; pimozide, zotepine, risperidone, olanzapine, quetiapine or amisulpride; especially drugs are 1 - 3 (preferably 2) typical antipsychotic drugs selected from chlorpromazine, haloperidol) and perphenazine and one atypical antipsychotic drug selected from risperidone, olanzapine, quetiapine and amisulpride) (all claimed).

ADVANTAGE - (I) Acts as a potent and highly safe drug therapy.
Dwg.0/0

- L52 ANSWER 3 OF 8 MEDLINE on STN DUPLICATE 2
2002400655 Document Number: 22057738. PubMed ID: 12063084. The antipsychotic aripiprazole is a potent, partial agonist at the human **5-HT_{1A} receptor**. **Jordan Shaun**; Koprivica Vuk; Chen Ruoyan; Tottori Katsura; **Kikuchi Tetsuro**; Altar C Anthony. (Neuroscience Department, Maryland Research Laboratories, Otsuka Maryland Research Institute, 9900 Medical Center Drive, Rockville, MD 20850, USA.. shaunj@otsuka.com) . EUROPEAN JOURNAL OF PHARMACOLOGY, (2002 Apr 26) 441 (3) 137-40. Journal code: 1254354. ISSN: 0014-2999. Pub. country: Netherlands. Language: English.
- AB Aripiprazole, 7-[4-[4-(2,3-dichlorophenyl)-1-piperazinyl]butyloxy]-3,4-dihydro-2(1H)-quinolinone, a novel antipsychotic with partial agonist activity at dopamine D₂ **receptors**, bound with high affinity to recombinant human **5-HT(1A) receptors** (h5-HT(1A)) in Chinese hamster ovary cell membranes and displayed potent, partial agonism at **5-HT(1A) receptors** in a guanosine-5'-O-(3-[(35)S]thio)-triphosphate ([(35)S]GTP gamma S)-binding assay that was blocked completely by a selective **5-HT(1A) receptor** antagonist. An interaction with **5-HT(1A) receptors** may contribute to the overall efficacy of aripiprazole against symptoms of schizophrenia, including anxiety, **depression**, cognitive and negative symptoms, and to its favorable side-effect profile. Combined with previous studies demonstrating the potent partial agonism of aripiprazole at dopamine D₂ **receptors**, this study suggests aripiprazole is the first dopamine-serotonin system stabilizer.
- L52 ANSWER 4 OF 8 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
2003:293642 Document No.: PREV200300293642. BEHAVIORAL STUDIES OF OPC - 14523, A NOVEL **ANTIDEPRESSANT**: ANTI - STRESS AND ANTI - OBSESSIVE COMPULSIVE DISORDER (OCD) EFFICACY. Yamada, S. (1); Uwahodo, Y. (1); Tottori, K. (1); **Kikuchi, T. (1)**; Mori, T. (1). (1) Research Inst. of Pharmacological and Therapeutical Development, Otsuka Pharmaceutical Co., Ltd., Tokushima, Japan Japan. Society for Neuroscience Abstract Viewer and Itinerary Planner, (2002) Vol. 2002, pp. Abstract No. 307.6. <http://sfn.scholarone.com>. cd-rom. Meeting Info.: 32nd Annual Meeting of the Society for Neuroscience Orlando, Florida, USA November 02-07, 2002 Society for Neuroscience. Language: English.
- AB OPC-14523 is a novel compound with sigma and **5-HT_{1A} receptor** agonistic and **5-HT** reuptake inhibitory activities, and shows **antidepressant**-like effects in animal models. In this study, we investigated the therapeutic and side-effect potential of OPC-14523 using animal models, and compared with those of selective serotonin reuptake inhibitors (SSRIs), such as fluoxetine, sertraline and paroxetine, and serotonin/noradrenaline reuptake inhibitors (SNRIs), such as venlafaxine and milnacipran.) OPC-14523 (30 and 100 mg/kg, p.o.) significantly inhibited abnormal eating behavior induced by tail-pinch stress in male Wistar rats, a putative model of bulimia nervosa. The inhibitory effect of OPC-14523 was partially antagonized by the sigma **receptor** antagonist NE-100, but not by

the **5-HT_{1A} receptor** antagonist NAN-190. SSRIs also reduced abnormal eating behavior, but SNRIs were inactive in this model. The anti-obsessive-compulsive disorder (OCD) effects were examined using marble-burying behavior in mice. OPC-14523 (30 and 100 mg/kg, p.o.), as well as SSRIs and SNRIs, significantly suppressed the number of marbles buried in sawdust. The suppression of marble-burying behavior was antagonized by NAN-190, but not by NE-100. In addition, we examined the effects of OPC-14523 on cognitive function using the Morris water maze. OPC-14523 did not impair spatial memory function, unlike fluoxetine.) These preclinical data predict that OPC-14523 may be effective in a broader range of psychiatric indications, including bulimia nervosa and OCD, without inducing cognitive dysfunction.

L52 ANSWER 5 OF 8 MEDLINE on STN DUPLICATE 3
2001700242 Document Number: 21615562. PubMed ID: 11747902.

Antidepressant-like responses to the combined sigma and 5 **-HT_{1A} receptor** agonist OPC-14523. Tottori K; Miwa T; Uwahodo Y; Yamada S; Nakai M; Oshiro Y; **Kikuchi T**; Altar C A. (Research Institute of Pharmacological and Therapeutical Development, Otsuka Pharmaceutical Co., Ltd, 463-10 Kagasuno 771-0192, Kawauchi-cho Tokushima, Japan.. k.tottori@research.otsuka.co.jp) . NEUROPHARMACOLOGY, (2001 Dec) 41 (8) 976-88. Journal code: 0236217. ISSN: 0028-3908. Pub. country: England: United Kingdom. Language: English.

AB The **antidepressant**-like activity of a novel compound, OPC-14523, was investigated in comparison with the conventional **antidepressants**, fluoxetine and imipramine. OPC-14523 bound with nanomolar affinities to sigma **receptors** (IC₅₀=47-56 nM), the **5-HT_{1A} receptor** (IC₅₀=2.3 nM), and the **5-HT** transporter (IC₅₀=80 nM). OPC-14523 inhibited the in vitro reuptake of 3H-**5-HT** (IC₅₀=27 nM), but it showed very weak inhibitory activity on 3H-NE and 3H-DA reuptake. OPC-14523 did not inhibit MAO A or B activities or muscarinic **receptors**. A single oral administration of OPC-14523 produced a marked **antidepressant**-like effect in the forced swimming test (FST) with rats (ED₅₀=27 mg/kg) and mice (ED₅₀=20mg/kg) without affecting the general locomotor activity. In contrast, fluoxetine and imipramine each required at least four days of repeated dosing to show this activity. The acute activity of OPC-14523 was blocked by pretreatment with the sigma **receptor** antagonist NE-100 or the selective **5-HT_{1A} receptor** antagonist WAY-100635. The induction of flat body posture by OPC-14523 was blocked by the selective **5-HT_{1A} receptor** antagonist NAN-190, and forebrain **5-HT** biosynthesis was attenuated by OPC-14523 at behaviorally effective doses. In contrast, OPC-14523, unlike fluoxetine, failed to inhibit **5-HT** reuptake at oral doses below 100mg/kg. Thus, the acute **antidepressant**-like action of OPC-14523 is achieved by the combined stimulation of sigma and **5-HT_{1A} receptors** without inhibition of **5-HT** reuptake in vivo.

L52 ANSWER 6 OF 8 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
2001:135108 Document No.: PREV200100135108. Role for sigma and 5-**HT_{1A} receptors** in the forced swimming test: supporting the mechanism of action of OPC-14523. Yamada, S. (1); Uwahodo, Y.; Tottori, K.; **Kikuchi, T.**; Altar, C. A.. (1) Otsuka Pharmaceutical Co. Ltd., Tokushima Japan. Society for Neuroscience Abstracts, (2000) Vol. 26, No. 1-2, pp. Abstract No.-871.7. print. Meeting Info.: 30th Annual Meeting of the Society of Neuroscience New Orleans, LA, USA November 04-09, 2000 Society for Neuroscience. ISSN: 0190-5295.

Language: English. Summary Language: English.

AB OPC-14523 is a novel synthetic compound with sigma and 5-HT1A receptor agonistic activities and 5-HT reuptake inhibitory activity. OPC-14523 has demonstrated antidepressant-like effects in the forced swimming test (FST) in rodents. The effect of OPC-14523 was almost completely antagonized by either a sigma receptor antagonist or 5-HT1A receptor antagonists in the FST. Therefore, we further investigated the interaction between sigma and 5-HT1A receptors in a modified version of Porsolt's rat FST. The immobility time of male Wistar rats was measured for 5 min using an auto activity analysis system. 5-HT and 5-HIAA levels in the frontal cortex and hippocampus were measured after the FST. (+)-Pentazocine (10 mg/kg), a sigma 1 receptor agonist, or 8-OH-DPAT (0.1 mg/kg), a 5-HT1A receptor agonist, significantly decreased immobility time in rat FST. The 5-HT1A receptor antagonist WAY-100635 blocked the decrease in immobility time induced by 8-OH-DPAT, but did not affect the decrease in immobility time induced by (+)-pentazocine. The combination of (+)-pentazocine with 8-OH-DPAT further reduced immobility time in the FST compared to each treatment, indicating an additive effect of the two drugs. These data suggest that sigma and 5-HT1A receptors independently exert antidepressant-like effects in the rat FST. Furthermore, these findings support prior evidence that the antidepressant-like effects of OPC-14523 are mediated by its agonistic activity at both sigma and 5-HT1A receptors.

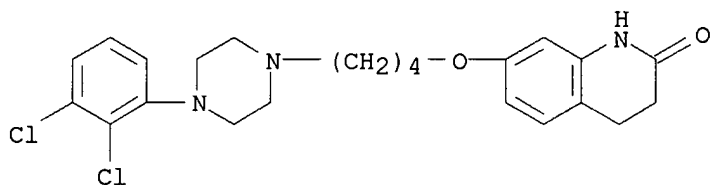
L52 ANSWER 7 OF 8 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN 2001:110538 Document No.: PREV200100110538. The antidepressant drug candidate OPC-14523 is a partial agonist at rat and recombinant human 5-HT1A receptors. Jordan, S. (1); Koprivica, V.; Altar, C. A.. (1) Otsuka America Pharmaceut Inc, Rockville, MD USA. Society for Neuroscience Abstracts, (2000) Vol. 26, No. 1-2, pp. Abstract No.-387.13. print. Meeting Info.: 30th Annual Meeting of the Society of Neuroscience New Orleans, LA, USA November 04-09, 2000 Society for Neuroscience. ISSN: 0190-5295. Language: English. Summary Language: English.

AB OPC-14523 is in Phase II clinical trials in the USA for the treatment of depression. This drug binds with high affinity to 5-HT1A (IC50 apprx 2 nM) and sigma receptors (IC50 apprx 30 nM), and its potent activity in rodent models predictive of antidepressant drug efficacy depends upon its 5-HT1A and sigma receptor agonism. In vitro (35S)GTP-gamma-S binding methods were used to determine the intrinsic efficacy (relative to 5-HT) of OPC-14523 at 5-HT1A receptors in rat brain sections and at the human 5-HT1A receptor (h5-HT1A) in CHO cell membranes. All reactions proceeded for 60 min at room temperature in a Tris-HCl buffer containing (35S)GTP-gamma-S, GDP and test drugs. Quantitative autoradiography and scintillation counting were used to measure (35S)GTP-gamma-S binding in transverse brain sections (20 mum) and h5-HT1A membranes, respectively. 5-HT and 5-carboxyamidotryptamine (5-CT) stimulated basal (35S)GTP-gamma-S binding in 5-HT1A/1B-containing brain regions by up to apprx75% and 95%, respectively. (+)8-OH-DPAT exhibited an intrinsic agonist efficacy of apprx85% and partial agonist responses were produced by OPC-14523 and buspirone. These drug effects were all abolished by WAY-100635, which was inactive on its own. The partial agonist efficacy of OPC-14523 and buspirone was also evident in their inhibition of

RN 129722-12-9 REGISTRY
CN 2(1H)-Quinolinone, 7-[4-[4-(2,3-dichlorophenyl)-1-piperazinyl]butoxy]-3,4-dihydro- (9CI) (CA INDEX NAME)

OTHER NAMES:

CN 7-[4-[4-(2,3-Dichlorophenyl)-1-piperazinyl]butoxy]-3,4-dihydrocarbostyrl
CN Abilitat
CN Aripiprazole
CN OPC 14597
CN OPC 31
FS 3D CONCORD
DR 156680-99-8
MF C23 H27 Cl2 N3 O2
CI COM
SR CA
LC STN Files: ADISINSIGHT, ADISNEWS, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CANCERLIT, CAPLUS, CASREACT, CHEMCATS, CIN, DDFU, DIOGENES, DRUGNL, DRUGPAT, DRUGU, DRUGUPDATES, EMBASE, IPA, MEDLINE, MRCK*, PHAR, PROMT, RTECS*, SYNTHLINE, TOXCENTER, USAN, USPATFULL
(*File contains numerically searchable property data)
Other Sources: WHO



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

64 REFERENCES IN FILE CA (1937 TO DATE)
1 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
68 REFERENCES IN FILE CAPLUS (1937 TO DATE)

=> s OPC 14523
147 OPC
45 14523
L2 1 OPC 14523
(OPC(W)14523)

=> d 12

L2 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2003 ACS on STN
RN 145969-30-8 REGISTRY
CN 2(1H)-Quinolinone, 1-[3-[4-(3-chlorophenyl)-1-piperazinyl]propyl]-3,4-dihydro-5-methoxy- (9CI) (CA INDEX NAME)

OTHER NAMES:

CN OPC 14523
FS 3D CONCORD
MF C23 H28 Cl N3 O2
CI COM
SR CA
LC STN Files: ADISINSIGHT, BIOSIS, CA, CAPLUS, CASREACT, DRUGNL, DRUGUPDATES, PHAR, PROMT, SYNTHLINE, TOXCENTER, USPAT2, USPATFULL

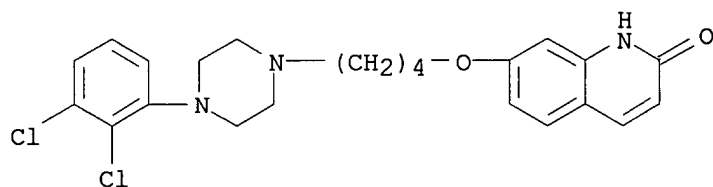
The IALL format is the same as ALL with BIB ABS and IND indented, with text labels.

For additional information, please consult the following help messages:

HELP DFIELDS -- To see a complete list of individual display fields.
HELP FORMATS -- To see detailed descriptions of the predefined formats.
ENTER DISPLAY FORMAT (IDE):end

=> d ide cbib abs

L27 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2003 ACS on STN
RN 129722-25-4 REGISTRY
CN 2(1H)-Quinolinone, 7-[4-[4-(2,3-dichlorophenyl)-1-piperazinyl]butoxy]-
(9CI) (CA INDEX NAME)
FS 3D CONCORD
MF C23 H25 Cl2 N3 O2
SR CA
LC STN Files: CA, CAPLUS, TOXCENTER, USPATFULL

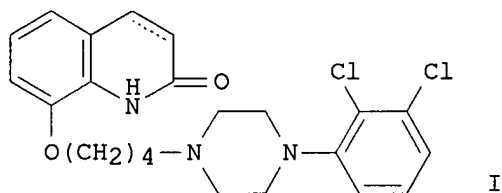


PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

4 REFERENCES IN FILE CA (1937 TO DATE)
4 REFERENCES IN FILE CAPLUS (1937 TO DATE)

REFERENCE 1: 137:363096 Carbostyryl derivative 5-HT1a receptor subtype agonist for treatment of central nervous system disorders. Jordan, Shaun; Kikuchi, Tetsuro; Tottori, Katsura; Hirose, Tsuyoshi; Uwahodo, Yasufumi (USA). U.S. Pat. Appl. Publ. US 2002173513 A1 20021121, 8 pp. (English). CODEN: USXXCO. APPLICATION: US 2002-55915 20020128. PRIORITY: US 2001-PV331370 20010129.

GI



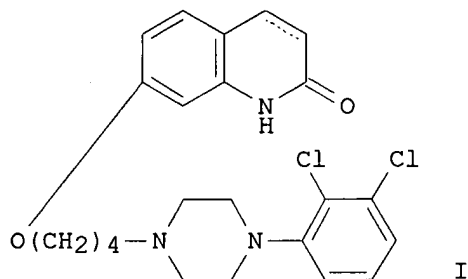
AB The invention provides a method for treating a patient suffering from a disorder of the central nervous system assocd. with the 5-HT1a receptor subtype, comprising as an active ingredient a carbostyryl deriv. I (carbon-carbon bond between 3- and 4-positions in carbostyryl skeleton is

Searched by: Mary Hale 308-4258 CM-1 1E01

single or double bond), or a salt thereof.

REFERENCE 2: 137:150248 Carbostyryl derivative 5-HT_{1A} receptor agonists for treatment of central nervous system disorders. Jordan, Shaun; Kikuchi, Tetsuro; Tottori, Katsura; Hirose, Tsuyoshi; Uwahodo, Yasufumi (Otsuka Pharmaceutical Co., Ltd., Japan). PCT Int. Appl. WO 2002060423 A2 20020808, 31 pp. DESIGNATED STATES: W: AU, BR, CA, CN, ID, IN, JP, KR, MX, PH, SG; RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2002-JP626 20020129. PRIORITY: US 2001-770210 20010129.

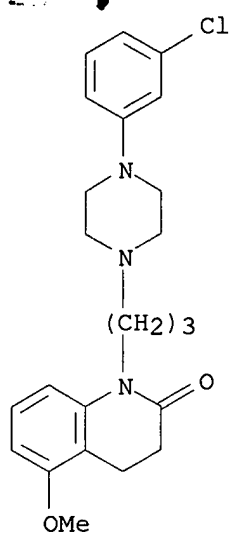
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AB The invention discloses the use of a compd. for the prodn. of a medicament for treating a patient suffering from a disorder of the central nervous system assocd. with 5-HT_{1A} receptor subtype, the medicament including as an active ingredient a carbostyryl deriv. I (C-C bond between 3- and 4-positions in the carbostyryl skeleton is single or double bond), or a pharmaceutically acceptable salt or solvate thereof.

REFERENCE 3: 128:175797 Novel Antipsychotic Agents with Dopamine Autoreceptor Agonist Properties: Synthesis and Pharmacology of 7-[4-(4-Phenyl-1-piperazinyl)butoxy]-3,4-dihydro-2(1H)-quinolinone Derivatives. Oshiro, Yasuo; Sato, Seiji; Kurahashi, Nobuyuki; Tanaka, Tatsuyoshi; Kikuchi, Tetsuro; Tottori, Katsura; Uwahodo, Yasufumi; Nishi, Takao (Third Institute of New Drug Research, Otsuka Pharmaceutical Company Ltd., Tokushima, 771-01, Japan). Journal of Medicinal Chemistry, 41(5), 658-667 (English) 1998. CODEN: JMCMAR. ISSN: 0022-2623. Publisher: American Chemical Society.

AB To develop a novel antipsychotic agent which is an agonist of dopamine (DA) autoreceptors and an antagonist of postsynaptic DA receptors, a series of 7-[4-[4-(substituted phenyl)-1-piperazinyl]butoxy]-3,4-dihydro-2(1H)-quinolinones was synthesized and their dual activities were examd. The postsynaptic DA receptor antagonistic activities of the compds. were evaluated by their ability to inhibit stereotypy induced by apomorphine in mice, and the autoreceptor agonist activities were detd. by their effects on the .gamma.-butyrolactone (GBL)-induced increase in L-dihydroxyphenylalanine (DOPA) synthesis in the mouse brain. Many compds. inhibited the stereotypic behavior, and several compds. reversed the GBL-induced increase in the DOPA synthesis. Among them, 7-[4-[4-(2,3-dichlorophenyl)-1-piperazinyl]butoxy]-3,4-dihydro-2(1H)-quinolinone (aripiprazole, OPC-14597) (I) had these 2 activities. This compd. reversed the GBL-induced DOPA synthesis (ED₅₀ values of 5.1 .mu.mol/kg po) and inhibited the APO induced stereotypy (ED₅₀ values of 0.6 mmol/kg po). I induced catalepsy at 10-fold higher dose than that required for the antagonism of APO-induced stereotypy (ED₅₀ value of 7.8 .mu.mol/kg oral).



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

6 REFERENCES IN FILE CA (1937 TO DATE)
6 REFERENCES IN FILE CAPLUS (1937 TO DATE)

=>

FILE 'HOME' ENTERED AT 17:38:20 ON 20 SEP 2003

=> e registry

THIS COMMAND NOT AVAILABLE IN THE CURRENT FILE

The EXPAND command is used to look at the index in a file which has an index. This file does not have an index.

=> s POC 14597

THIS COMMAND NOT AVAILABLE IN THE CURRENT FILE

Some commands only work in certain files. For example, the EXPAND command can only be used to look at the index in a file which has an index. Enter "HELP COMMANDS" at an arrow prompt (=>) for a list of commands which can be used in this file.

=> file registry

'REGISTRY' IS NOT A VALID FILE NAME

SESSION CONTINUES IN FILE 'HOME'

Enter "HELP FILE NAMES" at an arrow prompt (=>) for a list of files that are available. If you have requested multiple files, you can specify a corrected file name or you can enter "IGNORE" to continue accessing the remaining file names entered.

=> s OPC 14597

THIS COMMAND NOT AVAILABLE IN THE CURRENT FILE

Some commands only work in certain files. For example, the EXPAND command can only be used to look at the index in a file which has an index. Enter "HELP COMMANDS" at an arrow prompt (=>) for a list of commands which can be used in this file.

=> file registry

COST IN U.S. DOLLARS

SINCE FILE

TOTAL

ENTRY

SESSION

FULL ESTIMATED COST

0.42

0.42

FILE 'REGISTRY' ENTERED AT 17:39:26 ON 20 SEP 2003

USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.

PLEASE SEE "HELP USAGETERMS" FOR DETAILS.

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STRUCTURE FILE UPDATES: 19 SEP 2003 HIGHEST RN 589489-00-9

DICTIONARY FILE UPDATES: 19 SEP 2003 HIGHEST RN 589489-00-9

TSCA INFORMATION NOW CURRENT THROUGH JULY 14, 2003

Please note that search-term pricing does apply when conducting SmartSELECT searches.

Crossover limits have been increased. See HELP CROSSOVER for details.

Experimental and calculated property data are now available. See HELP PROPERTIES for more information. See STNote 27, Searching Properties in the CAS Registry File, for complete details:

<http://www.cas.org/ONLINE/STN/STNOTES/stnotes27.pdf>

=> s OPC 14597

147 OPC

44 14597

L1 1 OPC 14597

(OPC(W)14597)

=> d 11

L1 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2003 ACS on STN